ICF Consulting Review of NPB AEL Recommendation
Proposed by Environ Corporation

Introduction

ICF Consulting has been asked to review a letter report documenting the development of an acceptable exposure limit (AEL) for occupational exposure to NPB commissioned by Enviro Tech International and conducted by Environ Corporation (2002). In this report, Environ developed their own AEL, and reviewed the AEL derivations conducted by Drs. Doull and Rozman and by ICF Consulting. It was not clear if the author of Environ's report had also reviewed the original experimental studies that Rozman and Doull and ICF Consulting considered in their development of AEL values. Environ's analysis also presents criticisms of ICF's AEL derivation.

The Environ analysis identifies reduced sperm motility in the F0[1] generation of the two-generation reproductive study as the appropriate point of departure (POD) for deriving an AEL. Environ then applies an uncertainty factor (UF) of 3-4 to account for human variability and extrapolation from animal to human. This results in an AEL of 60-88 ppm, which as the author states, matches that proposed by Drs. Doull and Rozman.

Selection of Points of Departure

Environ selected the BMDL[2] for reduced sperm motility in the F0 generation as the appropriate POD for AEL derivation. Environ states that ICF's selection of reduced sperm motility in the F1 generation is questionable, stating that use of this endpoint would be appropriate for identifying exposures intended to be safe for the general population, but that an AEL is intended to protect the health of adult workers and need not be protective of children. The author states that since the F1 generation is exposed from conception through adulthood, the exposure likely exaggerates the sensitivity of the F1 animals compared to the occupational group that the AEL is intended to protect. The author goes on to state that this is likely a result of chemical exposure during the critical developmental phases before and shortly after birth, and is not relevant to occupational exposures. Environ then concludes that the BMDL from the F0 generation is the appropriate POD. ICF disagrees with this conclusion since the available data are not sufficient to elucidate when the adverse effects from nPB manifest. Specifically, it is impossible to determine for certain whether or not the F1 generation manifested their adverse reproductive effects based on exposure *in utero*, after birth but before maturity, or because of effects on the F0 parents.

ICF believes that the appropriate POD is the BMDL from the F1 generation, and not the F0 generation as suggested by Environ. First, under EPA's risk assessment guidelines, one uses the most sensitive endpoint; thus, it is appropriate to use the F1 generation. Further, nPB's mode

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1 From the two-generation animal study conducted by WIL Laboratories (2001)

2 The 95th percentile lower confidence limit on the benchmark dose

of action in causing reproductive effects has not been characterized, so potential transgenerational effects, such as endocrine disruption or other hormonal effects, cannot be ruled out. Thus, ICF finds that using the BMDL for the F0 generation as the POD is not sufficiently protective, and that the F1 generation should be used as the POD.

Choice of Uncertainty Factors

The author agrees with ICF's conclusion that among healthy workers, some individuals might have reduced reproductive capacity, and suggests that an UF of 2 might be applied to account for this. However, Environ states that ICF's application of an UF of 3 accounting for animal to human extrapolation (i.e., pharmacodynamics and pharmacokinetics) is flawed because it implicitly assumes a traditional UF of 10 is necessary for protection of "average" individuals. ICF can find no clear reason why the author believes that an UF of 10 is inappropriate in this case. Further, in the typical development of Reference Concentrations (RfC), an UF of 10 is used to extrapolate from the animal to a "typical" human; an additional uncertainty factor is then applied to account for variation within humans, or "sensitive subpopulations." Moreover, Environ provides no justification, other than the "less restrictive" guidelines of OSHA and ACGIH for occupational exposure, for using a lower UF than 10. The author correctly states that ICF, using EPA's RfC Guidelines (1994), reduced the UF for pharmacokinetics from 3 to 1. This is appropriate and in accordance with RfC Guidelines because blood:air partition coefficients suggest that the uptake of nPB in the rat is slightly higher than in the human. The author goes one step further to propose that this is sufficient reason to reduce the UF for pharmacokinetics to less than one based on the "delivered dose" discussion in ICF's development of an AEL. It is unclear why Environ believes that using a UF of less than one for animal to human extrapolation is reasonable, and ICF disagrees with this approach. First, utilizing an UF of less than one is contrary to EPA guidelines and to the manner in which AELs have been developed for other chemicals under the SNAP program. Second, other than the reported blood::air partition coefficients, data on distribution and transport of inhaled nPB or its metabolites in the human and the rat are not sufficient to support this approach. Finally, ICF is unaware of any case where an UF of less than one has been applied as a general practice in the absence of data to support it. In order to support this choice, complete information regarding pharmacokinetics of nPB in both the rat and the human would be necessary.

Based on the above reasoning, Environ concludes that a total UF of 3-4 is appropriate. ICF believes that the reasoning behind this UF range is flawed and that a total UF of 3-4 is not sufficiently protective of worker health.

Additional UF for Reproductive Effects

Environ also responds to an assertion made by Enviro Tech International. The author states "In discussions with me [Environ], you [Enviro Tech] stated that some scientists at USEPA believe that additional UFs are traditionally included to deal specifically with reproductive effects." This statement is incorrect. ICF in its AEL derivation delivered to EPA, did not apply an additional UF specific to reproductive effects. ICF did apply a UF to account for sensitive subpopulations within the working population (e.g., men with low sperm count). ICF believes

that this UF is appropriate because men with reproductive deficits would appear overtly healthy and would not be precluded from the workplace. The author states, "I have at present, no clear reason to reject the argument that, among healthy workers, some might have more limited reproductive capacity, so accept that a UF of 2 might be appropriate." Thus, Environ appears to agree with ICF on this point.

Conclusion

ICF believes that the Environ approach to setting an occupational exposure limit is flawed for the following reasons. First, based on the available data, transgenerational effects arising from nPB exposure in both males and females cannot be discounted. Thus, it is necessary to use the most sensitive endpoint identified from the database, in this case reduced sperm motility in the F1 generation. Second, ICF believes that a total UF of 3-4 is insufficient to protect human health, and that an UF of 3 for pharmacodynamics, and 2-3 for sensitive subpopulations is necessary. Further, Environ's suggestion of reducing the UF for pharmacokinetics to less than one is not supported by data and is contrary to EPA's risk assessment guidelines. Finally, ICF did not use an additional UF specific to reproductive effects, but appropriately applied an UF to protect sensitive subpopulations within the working population.

References

Kim Y., Jung K., Hwang T., Jung G., Kim H., Park J., Kim J., Park J., Park D., Park S., Choi K., Moon Y. 1996. Hematopoietic and reproductive hazards of Korean electronic workers exposed to solvents containing 2-bromopropane. Scand J Work Environ Health 22:387-391.